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Antiepileptic drug monotherapy for epilepsy in the elderly: a systematic review and network meta-analysis

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Summary

Objective: To estimate the comparative efficacy and safety of antiepileptic drugs (AEDs) in elderly with new-onset epilepsy.

Methods: We searched electronic databases for randomized controlled trials (RCTs) of monotherapy AEDs to treat epilepsy in elderly. The following outcomes were analyzed: seizure freedom and withdrawal from the study for any cause at 6 and 12 months; withdrawal from the study for any adverse event (AE) at 12 months; occurrence of any AE at 12 months. Effect sizes were estimated by network meta-analyses within a frequentist framework. The hierarchy of competing interventions was established using the surface under the cumulative ranking curve (SUCRA) and mean ranks.

Results: Five RCTs (1,425 patients) were included. Included AEDs were: carbamazepine immediate- and controlled- release (CBZ-IR, CBZ-CR), gabapentin (GBP), lacosamide (LCM), lamotrigine (LTG), levetiracetam (LEV), phenytoin (PHT), and valproic acid (VPA). At the pairwise and network meta-analyses, there were no differences in any of the comparison according to 6- and 12-month seizure freedom. The treatment with CBZ-IR and CBZ-CR was associated with a higher risk of withdrawal than LTG, LEV or VPA, and CBZ-IR had the overall highest probability of discontinuation across all AEDs. According to SUCRA, LCM, LTG, and LEV had the greatest likelihood ranking best for seizure freedom at 6 and 12 months. CBZ-CR and CBZ-IR had the highest probabilities of being worst for the 12-month retention. CBZ-IR, CBZ-CR and GBP had the highest probabilities of withdrawal from the study for AEs~~,~~ and VPA had the highest probability to be the best tolerated option.

Significance: Although no significant difference in efficacy was found across treatments, LCM, LTG and LEV had the highest probability of ranking best for achieving seizure freedom. CBZ-IR and CBZ-CR showed a poor tolerability profile leading to higher withdrawal rates compared to LEV and VPA.

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Key Points:

- In this systematic review we estimated the comparative efficacy and safety of antiepileptic drugs in elderly with new-onset epilepsy.
- No differences were found for 6- and 12-month seizure freedom, whilst CBZ-IR and CBZ-CR were withdrawn more frequently than other drugs.
- LCM, LTG and LEV had the highest probability of ranking best for achieving seizure freedom.
- CBZ-IR and CBZ-CR had a poor tolerability profile and higher withdrawal rates than LEV and VPA.

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1. Introduction

Epilepsy has a peak incidence in older age groups, with an annual incidence of 134 per 100,000 in people aged ≥ 65 years.[1] Due to the rapidly aging population, epilepsy in the elderly is increasingly encountered in clinical practice, and its incidence among this age group has actually increased in the recent decades.[2] In this population, cerebrovascular disease represents the most commonly identified etiology, along with dementia, brain tumors, and trauma.[3] The underlying cause remains, however, unknown in as many as 25-40% of the cases.[4]

The management of new-onset epilepsy in the elderly is challenging, as ageing affects drug pharmacokinetics and pharmacodynamics, and increases the risk of adverse events; polytherapy for medical and psychiatric comorbidities is also common and further raises the risk of drug interactions and poor medication adherence.[5,6] All these issues need to be carefully taken into account by physicians in the selection of the initial antiepileptic monotherapy. In this regard, the availability of data on the comparative efficacy and safety of antiepileptic drugs (AEDs) would provide useful clinical guidance for the management of elderly patients with new-onset epilepsy. So far, however, only few randomized controlled trials (RCTs) have been performed, and the evidence coming from direct head-to-head comparisons is limited.[7]

In this study, we aimed to systematically review the currently available RCTs of AEDs used as monotherapy treatment for epilepsy in elderly patients, and estimate their comparative efficacy and safety by means of a network meta-analysis (NMA).

2. Methods

Results were reported according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for network meta-analyses[8] (Appendix I). The review protocol was not previously registered.

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Randomized controlled trials comparing any AED versus any comparator as monotherapy for newly diagnosed (incident) epilepsy (any type) in elderly patients (≥60 years) were included. Studies with other design or conducted in etiology-specific epilepsy (e.g., stroke or Alzheimer´s disease) were not included in the current analysis.

The following electronic databases and data sources were systematically searched:

1.MEDLINE (January 1966–2nd June 2019), accessed through PubMed;

2.Cochrane Central Register of Controlled Trials (CENTRAL; accessed 2nd June 2019);

3.EMBASE (accessed 2nd June 2019);

4. Opengrey.eu (available at: www.opengrey.eu; accessed 2nd June 2019)

Details of the search strategy are reported in Appendix II. All resulting titles and abstracts were evaluated, and any relevant article was considered. No language restrictions were adopted.

Retrieved articles were independently assessed for inclusion by two review authors (FB, SL); any disagreement was resolved through discussion. The methodological quality of all included studies and the risk of bias were assessed as outlined in the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0[9] (Appendix III).

The following trial data were independently extracted by two review authors (FB, RN): main study author and date of publication; inclusion and exclusion criteria; number, age, and sex of participants for each treatment group; study phases; intervention details (tested drug and comparator). The following outcomes were considered:

Efficacy outcomes

1. seizure freedom (all seizure types) at 6 months (24 ± 2 weeks) and 12 months (52 ± 2 weeks) from the start of the maintenance phase;
2. withdrawal from the study for any cause at 6 months (24 ± 2 weeks) and 12 months (52 ± 2 weeks) from the start of the maintenance phase;

Safety outcomes

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1. Withdrawal from the study for any adverse event (AE) at 12 months from the start of the titration or maintenance phase;
2. Occurrence of any AE at 12 months from the start of the titration or maintenance phase.

First, we did pairwise meta-analyses for all outcomes, using a fixed-effects model. Second, we performed network meta-analyses within a frequentist framework assuming equal heterogeneity parameter τ across all comparisons.[10] It is appropriate to use NMA if the assumption of transitivity (distributions of the potential effect modifiers, like study and patient-level covariates, are balanced across all pairwise comparisons) can be defended.[11] We assessed the transitivity assumption looking at the similarities of studies in each comparison. Closed loops in the network were formed by multi-arm studies and, hence, we were not able to assess the agreement between direct and indirect evidence for a specific comparison (consistency assumption).[12] Effect sizes were estimated as odds ratios (ORs) with their 95% confidence intervals (CIs). The hierarchy of competing interventions was established using the surface under the cumulative ranking curve (SUCRA) and mean ranks. All analyses were intention-to-treat. Data analysis was performed using STATA/IC 13.1 statistical package (StataCorp LP, College Station, TX, USA).

3. Results

We identified a total of 2,349 records by database and trial registers searching (1,087 EMBASE, 930 MEDLINE, 321 CENTRAL, 11 Opengrey.eu). After excluding duplicates (1,213) and reading title and abstracts, 14 RCTs were initially considered. After reading the full-text, 9 studies were eventually excluded (see Appendix IV). Hence, 5 RCTs were included (Figure 1), which recruited 1,425 patients with newly diagnosed epilepsy.[13-18] One study[16] reported post-hoc analyses of elderly participants' data derived from a previous RCT[18]; one study, which included also younger participants, provided enough data on elderly

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patients to be analyzed separately.[17,19] The following comparisons were included in the RCTs: phenytoin (PHT) versus valproic acid (VPA),[13] carbamazepine-immediate release (CBZ-IR) versus lamotrigine (LTG) versus gabapentin (GBP),[14] carbamazepine-controlled release (CBZ-CR) versus LTG versus levetiracetam (LEV),[15] LEV versus VPA and LEV versus CBZ-CR,[16] and CBZ-CR versus lacosamide (LCM).[17,19] Characteristics of the included trials and study participants are summarized in Table 1 and Table 2, respectively.

3.1. Risk of bias of included studies.

A summary of risk of bias assessment is reported in Appendix V and VI. All studies defined the method used for random sequence generation, and 4 provided the details of allocation concealment.[14-17] One RCT did not perform a blinding of the participants and personnel (high risk of performance bias),[13] and one was unblinded (participants, study personnel, and outcome assessors; high risk of performance and detection bias).[16] Two studies were judged at high risk of selective reporting, as one was a post hoc analysis[16] and the other did not provide results of all the specified primary and secondary outcomes.[17]

3.2. Efficacy outcomes

Only 3 RCTs provided data on seizure freedom at 6 and 12 months; they compared CBZ-CR versus LTG versus LEV,[15] LEV versus VPA or LEV versus CBZ-CR,[16] and CBZ-CR versus LCM.[17,19] Figure 2 shows the network plots of treatment comparisons for the efficacy outcomes. At the pairwise meta-analyses, there were no differences in any of the comparison according to 6- and 12-month seizure freedom; CBZ-IR was associated with a higher rate of study withdrawal for any cause at 12 months than LTG (OR 2.29; 95% CI: 1.53 to 3.43) and GBP (OR: 0.57; 95% CI: 0.38 to 0.86), and LEV was associated with a lower risk of 12-month study discontinuation in comparison to CBZ-CR (OR: 0.40; 95% CI: 0.28 to 0.59).

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Also VPA was associated with a lower risk of study withdrawal for any cause at 12 months compared to CBZ-CR (OR: 0.34; 95% CI: 0.16 to 0.73) (Table e-1).

Results of the network meta-analyses of efficacy outcomes are shown in Figure 3. No significant differences were noted between AEDs in the achievement of seizure freedom at 6 months. There were non-significant trends favoring LCM over CBZ-CR (OR 1.79; 95% CI: 0.83 to 3.86) and LTG over CBZ-CR (OR 1.38; 95% CI: 0.85 to 2.24). Similarly, no statistically significant differences were found across treatments for seizure freedom at 12 months. A non-significant trend favoring LEV over CBZ-CR was found (OR 1.28; 95%CI: 0.89 to 1.85). According to SUCRA, LCM, LTG and LEV had the greatest likelihood ranking best for seizure freedom at 6 and 12 months (Table 3 and Appendix VII).

There was insufficient information on proportion of patients withdrawing from the study for any cause at 6 months to allow analyses. In comparison to CBZ-CR, LEV (0.40; 95% CI: 0.28 to 0.59), VPA (0.40; 95% CI: 0.19 to 0.83) and LTG (0.59; 95% CI: 0.37 to 0.96) were associated with a lower rate of 12-month withdrawal for any cause. There were higher withdrawal rates for GBP than for LEV (1.93; 95% CI: 1.03 to 3.61), and for CBZ-IR compared to LEV (3.36; 95% CI: 1.79 to 6.31), VPA (3.37; 95% CI: 1.34 to 8.49), and LTG (2.29; 95% CI: 1.53 to 3.43). GBP had a better retention rate than CBZ-IR (OR 0.57; 95% CI: 0.38 to 0.86). According to SUCRA, CBZ-CR and CBZ-IR had the highest probabilities of being worst for the 12-month retention.

3.3. Safety outcomes

All 5 RCTs provided data on withdrawal from the study for adverse events, whereas only 3 studies provided data on 12-month occurrence of AEs. Figure 2 shows the network plots of treatment comparisons for the safety outcomes. At the pairwise meta-analyses, LEV and VPA were associated with a lower risk of 12-month study withdrawal due to AEs than CBZ-CR (OR 0.33; 95% CI: 0.21 to 0.51 and OR: 020; 95% CI: 0.07 to 0.54, respectively); GBP had

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lower discontinuation rate than CBZ-IR (OR: 0.62; 95% CI: 0.39 to 0.97), whereas CBZ-IR and GBP had higher rates of discontinuation in comparison to LTG (OR: 3.27; 95% CI: 1.94 to 5.52 and OR 2.02; 95% CI: 1.17 to 3.48). The risk of AE occurrence at 12 months was lower with VPA than CBZ-CR (OR: 0.37; 95% CI: 0.17 to 0.79) (Table e-1).

Results of the network meta-analyses of efficacy outcomes are shown in Figure 3.

With regard to the outcome of 12-month study withdrawal due to AEs, LEV and VPA performed better than CBZ-CR (OR: 0.33; 95% CI: 0.21 to 0.51 and OR: 0.23; 95% CI: 0.08 to 0.61, respectively). CBZ-IR was associated with a higher rate of discontinuation than CBZ-CR (OR: 2.18; 95% CI: 1.03 to 4.61), LEV (OR: 6.68; 95% CI: 3.08 to 14.49), VPA (OR: 9.68; 95% CI: 2.87 to 32.65), and LTG (OR: 3.27; 95% CI: 1.94 to 5.52); GBP was associated with a higher risk of withdrawal than LEV (OR: 4.12; 95% CI: 1.87 to 9.08), VPA (OR: 5.96; 95% CI: 1.75 to 20.33), and LTG (OR: 2.01; 95% CI: 1.17 to 3.48). Treatment with LTG had a higher risk of 12-mont withdrawal than LEV (OR: 2.04; 95% CI: 1.15 to 3.62). According to SUCRA, CBZ-IR, CBZ-CR and GBP had the highest probabilities of withdrawal from the study for AEs (or, conversely, the lowest probability of being retained) (Table 3 and Appendix VII). VPA was associated with a lower risk of occurrence of AEs at 12 months in comparison to CBZ-CR (OR: 0.40; 95% CI: 0.20 to 0.82); conversely, LTG was associated with higher occurrence of AEs than VPA (OR: 4.23; 95% CI: 1.44 to 12.40). According to SUCRA, the use of VPA had the highest probabilities of being the best tolerated option.

4. Discussion

One main finding of the current study was the lack of any clear-cut difference across AEDs in their comparative efficacy, estimated as the likelihood of seizure freedom at 6 and 12 months, when given as monotherapy in new-onset epilepsy in the elderly. Although this might reflect lack of statistical power and false negative results,[20] equi-effectiveness should be considered.

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Remarkably, all the RCTs conducted so far in elderly with new-onset epilepsy and adopting a superiority design failed to demonstrate any difference with the active comparator, the only exception being one study showing a higher retention rate for LEV than for CBZ-CR, although without difference in seizure freedom.[15] Hence, the possibility that the efficacy profile across different AEDs is similar should not be disregarded. It is, however, also worth to notice that a not significant trend favoring LCM, LTG and LEV over CBZ-CR was found. The current NMA has also shown that the treatment with CBZ-IR and CBZ-CR was associated with a higher risk of withdrawal than LTG, LEV or VPA, and CBZ-IR had the overall higher probability of discontinuation across all treatment options. The use of extended-release CBZ is widely recommended to facilitate compliance, minimize peak and trough fluctuations, and obtain relatively stable blood concentrations, reducing the risk of AEs, and increasing the compliance by allowing once or twice daily intake.[21,22] However, these recommendations were based on pharmacokinetic considerations rather than clinical evidence, due to the lack of direct head-to-head comparisons between IR and CR formulations. In this regard, the current analyses provided indirect evidence to support the preferential use of CBZ-CR over CBZ-IR due to the lower risk of withdrawal due to AEs. We could not assess whether CBZ preparations used in the RCTs came from the same drug manufacturer, as this information was not explicitly reported in all studies (Appendix VIII). Furthermore, the included studies did not systematically measured CBZ serum levels, making it difficult to establish whether differences in absorption rates of CBZ across the studies may have contributed to the relatively poorer tolerability of this drug compared to other AEDs. This NMA is the first one to compare the efficacy and safety of AEDs used as monotherapy treatment for epilepsy in elderly patients, and updates and build up the currently available systematic reviews of evidence. In 2013, the Commission on Therapeutic Strategies of the International League Against Epilepsy (ILAE) has reviewed the available evidence of AEDs efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes in

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different age groups.[23] This review concluded that GBP and LTG have established (level of evidence: A) long-term efficacy or effectiveness as initial monotherapy for elderly with newly diagnosed or untreated epilepsy; CBZ was found to be possibly (level C), and topiramate and VPA as potentially (level D) efficacious/effective. However, no information on LEV and LCM was available at that time, as results of RCTs on these drugs had yet to be published. Very recently, a systematic review of the literature found that in elderly with new-onset epilepsy, LTG was better tolerated than CBZ, whereas LEV was associated with higher seizure freedom rates than LTG, without significant differences in tolerability; no significant differences were found between CBZ and LEV for efficacy and tolerability.[7] Notably, results of this review should be read with caution because of the wide entry criteria adopted (e.g., AEDs as monotherapy or add-on treatments) and the inclusion of RCTs that were very different in their clinical and methodological characteristics. Conversely, in the present NMA we used very strict inclusion criteria in order to minimize as much as possible any source of clinical and methodological heterogeneity, which could have resulted in an increased overall risk of inaccuracy. Some limits should be however considered while interpreting the findings, as the inclusion of a limited number of studies exploring only a set of the approved AEDs, the lack of data according to drug dosage, and the short length of the follow-up, which could not allow to identify long-term adverse events (e.g., parkinsonism associated with chronic VPA use[24,25]).

5. Conclusion

In conclusion, this study provides evidence that CBZ, either in its IR or CR formulation, has a poor tolerability profile leading to higher withdrawal rates compared to newer AEDs, mostly VPA and LEV. Although no significant difference in efficacy was found across treatments, LCM, LTG and LEV had the highest probability of ranking best for achieving seizure freedom. NMAs are not substitutes for clinical trials directly comparing two or more drugs,

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but they may offer reliable evidence of the relative efficacy and safety,[20,26] provide useful information about the hierarchy of competing interventions and represent a complementary guide to inform physicians in their clinical decision-making.

Disclosure of Conflicts of Interest

This study was not funded.

Francesco Brigo has acted as a paid consultant to Eisai and LivaNova, and received travel support from Eisai. Eugen Trinka has acted as a paid consultant to Eisai, EVER Neuro Pharma, Biogen Idec, Medtronics, Bial, and UCB and has received speakers' honoraria from Bial, Eisai, Boehringer Ingelheim, Biogen, Newbridge, Novartis, and UCB Pharma in the past 3 years. Eugen Trinka has received research funding from UCB Pharma, Biogen, Novartis, Bayer, Eisai, Red Bull, Merck, the European Union, FWF Österreichischer Fond zur Wissenschaftsförderung, and Bundesministerium für Wissenschaft und Forschung. Eugen Trinka is also part of the investigators planning the ESET Trial and member of the Task Force on Classification of Status Epilepticus of the International League Against Epilepsy (ILAE). Other Authors have no conflict of interest.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Figure and table legends

Figure 1: Study flow diagram

Figure 2: Network of treatment comparisons for efficacy and safety

Figure 3: Interval plots for the efficacy and safety outcomes

Table 1: Study characteristics

Table 2: Clinical characteristics of patients included in each trial

Table 3: Ranking according to SUCRA and mean rank for the efficacy and safety outcomes

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Supporting information:

Figure e-1. Two-dimensional graphs of efficacy versus tolerability at 12 months. The graphs include only treatments for which efficacy and safety data are available.

Table e-1: Results of the pairwise meta-analyses for the efficacy and safety outcomes

Appendix I: PRISMA checklist

Appendix II: Search strategy for different databases

Appendix III: Assessment of risk of bias, adopted from the Cochrane Handbook. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. Higgins JPT and Green S, editors. The Cochrane Collaboration, 2011. Available at http://handbook-5-1.cochrane.org/.

Appendix IV: List of excluded studies with reasons for exclusion

Appendix V: Summary of risk of bias in included studies: review authors' judgements about each risk of bias item for each included study.

Appendix VI: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

Appendix VII: Ranking according to SUCRA for the efficacy and safety outcomes

Appendix VIII: Details of carbamazepine preparation and manufacturing drug company

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Table 1: Study characteristics

Study	Study design	Inclusion criteria	Exclusion criteria	Comparisons, daily dose, mg/day [range] (participants, n)	Study duration, weeks; phases
Craig and Tallis, 1994[13]	Single center, randomised, study investigator and outcome assessor blinded trial	≥1 unprovoked GTCS or ≥ 2 focal seizures, age > 60 years	Progressive neurological disease	PHT mean 247 mg/day [175-275] (n=20) versus VPA mean 688 mg/day [400-1000] (n=18)	52 weeks
Rowan et al., 2005[14]	Multicentre, randomised, double-blind trial	Newly diagnosed epilepsy with seizures of any type, age ≥ 65 years	Progressive neurological disease	CBZ-IR 600 mg/day (n=198) versus LTG 150 mg/day (n=200) versus GBP 1500 mg/day (n=195)	52 weeks 1. Titration: 6 weeks 2. Maintenance: 46 weeks
Werhahn et al., 2015[15]	Multicentre, randomised, double-blind trial	Patients aged ≥60 years with new-onset focal epilepsy; no or <4 weeks previous AED treatment	Acute symptomatic seizures; previous treatment with VPA; renal insufficiency; increased liver enzymes or bilirubin; dementia; drug or alcohol abuse; psychiatric condition requiring legal guardianship; reduced life expectancy	CBZ-CR 400 mg/day (n=120) versus LTG 100 mg/day (n=117) versus LEV 1000 mg/day (n=122)	58 weeks 1. Titration: 6 weeks 2. Maintenance: 52 weeks
Pohlmann-Eden et al., 2016[16]	Multicentre, randomised, unblinded trial	Newly diagnosed, unprovoked seizures, age ≥16 years (limited to ≥ 60 years in our analysis)	Previous treatment with LEV, VPA or CBZ for any indication or treatment for epilepsy with any other AED in the last 6 months	Two parallel groups: LEV 1000 mg/day (n=48) versus VPA 1000 mg/day (n=52) LEV 1,000 mg/day (n=104) versus CBZ-CR 600 mg/day (n=103)	52 weeks 1. Titration: 2 weeks 2. Maintenance: 50 weeks
Baulac et al., 2017[17]; Rosenow et al., 2017[19]	Multicentre, randomised, double-blind, non-inferiority trial	Newly diagnosed, untreated epilepsy (focal unprovoked or GTCS), age ≥16 years (limited to ≥ 65 years in our analysis)	Seizure clusters or status epilepticus; conversion disorders or other non-epileptic ictal events; prior treatment with LCM or CBZ; drugs affecting CBZ metabolism; women not using contraception	CBZ-CR 400 mg/day (n=57) versus LCM 200 mg/day (n=62)	≥30 weeks 1. Screening: 1 week 2. Titration: 2 weeks 3. Stabilization: 1 week 4. Evaluation with flexible dosing: 26 weeks 5. Maintenance: 26 weeks

Abbreviations: AED: antiepileptic drug; CBZ: carbamazepine; CBZ-CR: carbamazepine controlled-release; CBZ-IR: carbamazepine immediate-release; GBP: gabapentin; GTCS: generalized tonic-clonic seizure; LCM: lacosamide; LEV: levetiracetam; LTG: lamotrigine; PHT: phenytoin; VPA: valproic acid.

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Publisher DOI: 0.1111/epi.16366

Table 2: Clinical characteristics of patients included in each trial

Study	Number of participants (ITT)	Proportion of women, %	Mean age, years, mean ± SD/ [range]
Craig and Tallis, 1994[13]	38	Not reported	PHT 74.9 [67-84] VPA 76.3 [62-88]
Rowan et al., 2005[14]	590	CBZ-IR 6.2% LTG 2.5% GBP 3.3%	CBZ-IR 71.9 ± 7.7 LTG 71.9 ± 7.4 GBP 72.9 ± 7.5
Werhahn et al., 2015[15]	359	CBZ-CR 45.8% LTG 41.0% LEV 33.6%	CBZ-CR 71.7 ± 6.7 LTG 70.7 ± 7.4 LEV 71.8 ± 7.5
Pohlmann-Eden et al., 2016[16]	307	Comparison LEV versus VPA: LEV 47.9% VPA 36.5% Comparison LEV versus CBZ-CR: LEV 42.3% CBZ-CR 47.6%	Comparison LEV versus VPA: LEV 71.1 ± 6.8 VPA-ER 70.4 ± 6.5 Comparison LEV versus CBZ-CR: LEV 68.8 ± 5.9 CBZ-CR 69.3 ± 6.4
Baulac et al., 2017;[17] Rosenow et al., 2017[19]	119	Not reported	≥ 65 years; no other details available

Abbreviations: CBZ: carbamazepine; CBZ-CR: carbamazepine controlled-release; CBZ-IR: carbamazepine immediate-release; GBP: gabapentin; ITT: intention-to-treat; LEV: levetiracetam; LTG: lamotrigine; PHT: phenytoin; SD: standard deviation; VPA: valproic acid.

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Table 3: Ranking according to SUCRA and mean rank for the efficacy and safety outcomes

a) Seizure freedom at 6 months

Treatment	SUCRA	Mean rank
CBZ-CR	15.9	4.4
LCM	81.5	1.7
LEV	54.9	2.8
VPA	34.6	3.6
LTG	63.2	2.5

b) Seizure freedom at 12 months

Treatment	SUCRA	Mean rank
CBZ-CR	25.1	4.0
LCM	71.9	2.1
LEV	68.1	2.3
VPA	34.6	3.6
LTG	50.4	3.0

c) Withdrawal for any cause at 12 months

Treatment	SUCRA	Mean rank
CBZ-CR	17.9	6.7
LCM	47.7	4.7
LEV	80.1	2.4
VPA	76.3	2.7
LTG	55.8	4.1
CBZ-IR	4.1	7.7
GBP	35.0	5.6
PHT	83.1	2.2

d) Withdrawal for any adverse event at 12 months

Treatment	SUCRA	Mean rank
CBZ-CR	35.2	5.5
LCM	51.1	4.4
LEV	85.5	2.0
VPA	94.5	1.4
LTG	58.5	3.9
CBZ-IR	3.4	7.8
GBP	24.0	6.3
PHT	47.7	4.7

e) Any adverse event at 12 months

Treatment	SUCRA	Mean rank
CBZ-CR	35.1	3.6
LCM	48.5	3.1
LEV	61.6	2.5

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VPA	96.6	1.1
LTG	8.2	4.7

Abbreviations**:** CBZ: carbamazepine; CBZ-CR: carbamazepine controlled-release; CBZ-IR: carbamazepine immediate-release; GBP: gabapentin; LCM: lacosamide; LEV: levetiracetam; LTG: lamotrigine; PHT: phenytoin; SUCRA: surface under the cumulative ranking curve; VPA: valproic acid.

Higher SUCRA values correspond to higher probabilities of better efficacy/tolerability.

Figure 1.

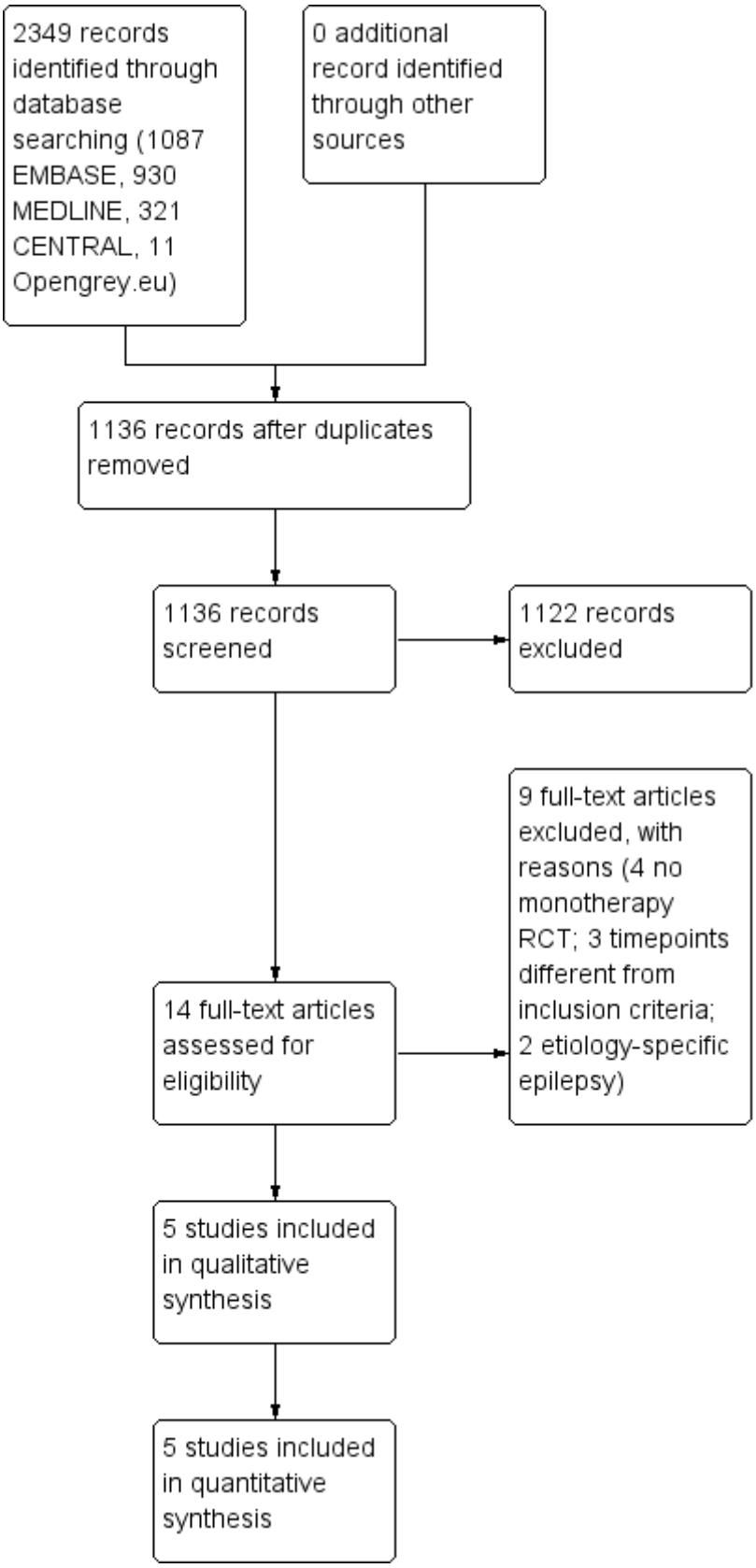
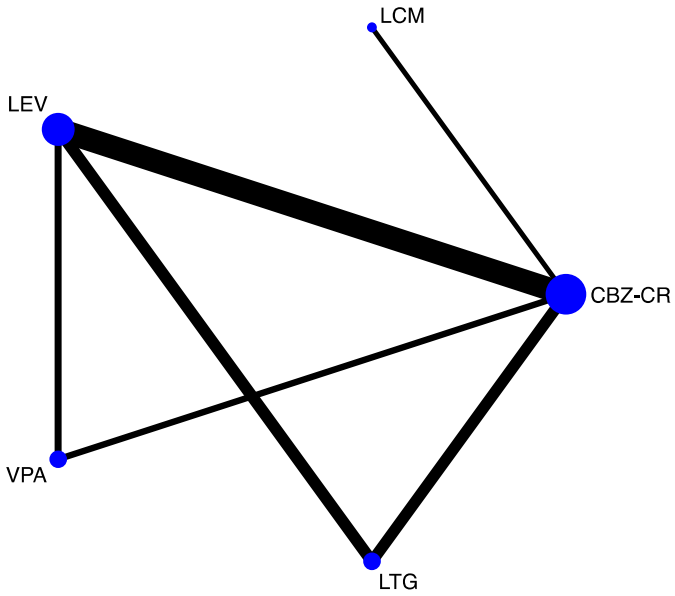
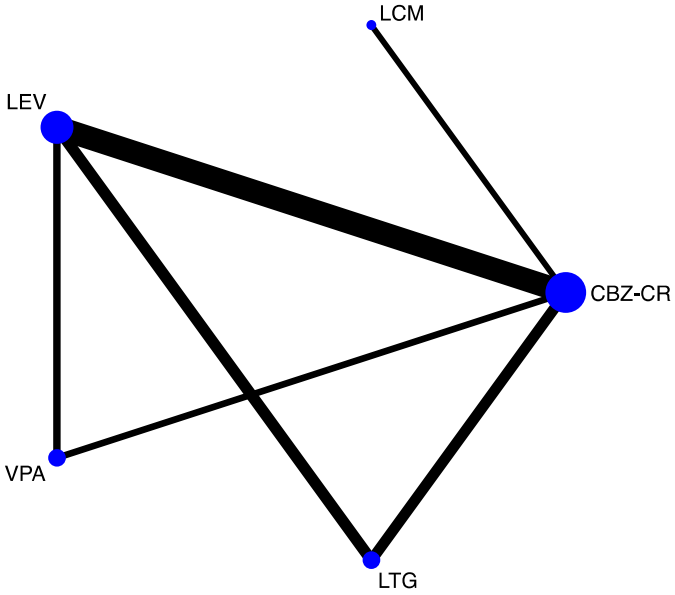

2349 records identified through database searching (1087 EMBASE, 930 MEDLINE, 321 CENTRAL, 11 Opengrey.eu)
0 additional record identified through other sources
1136 records after duplicates removed
1136 records screened
1122 records excluded
9 full-text articles excluded, with reasons (4 no monotherapy RCT; 3 timepoints different from inclusion criteria; 2 etiology-specific epilepsy)
14 full-text articles assessed for eligibility
5 studies included in qualitative synthesis
5 studies included in quantitative synthesis

Figure 2. Network of treatment comparisons for efficacy and safety outcomes

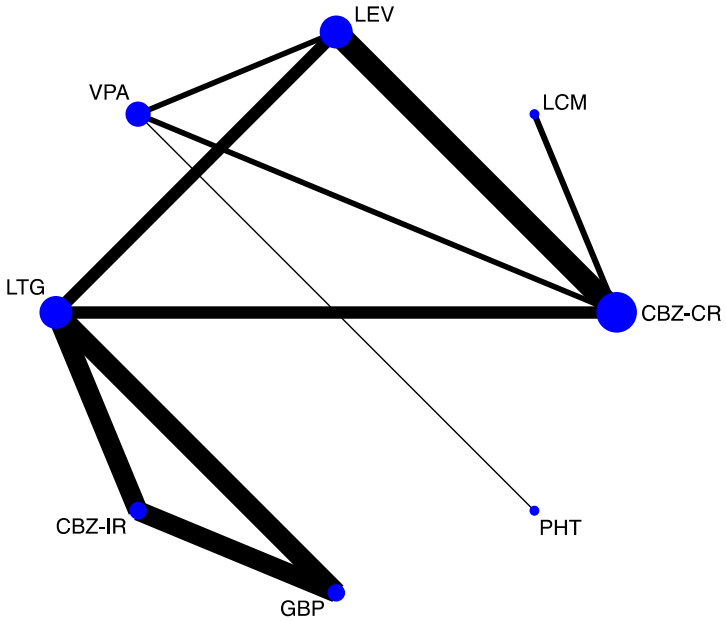
a) Seizure freedom at 6 months



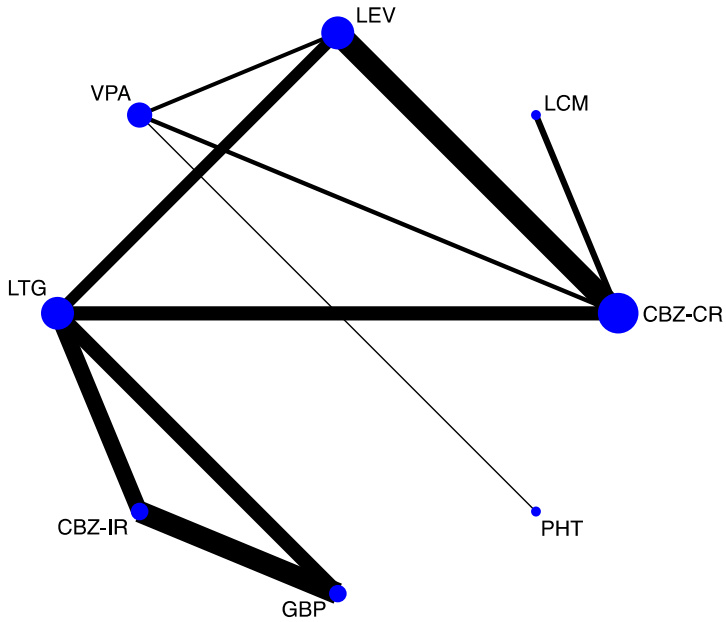
b) Seizure freedom at 12 months



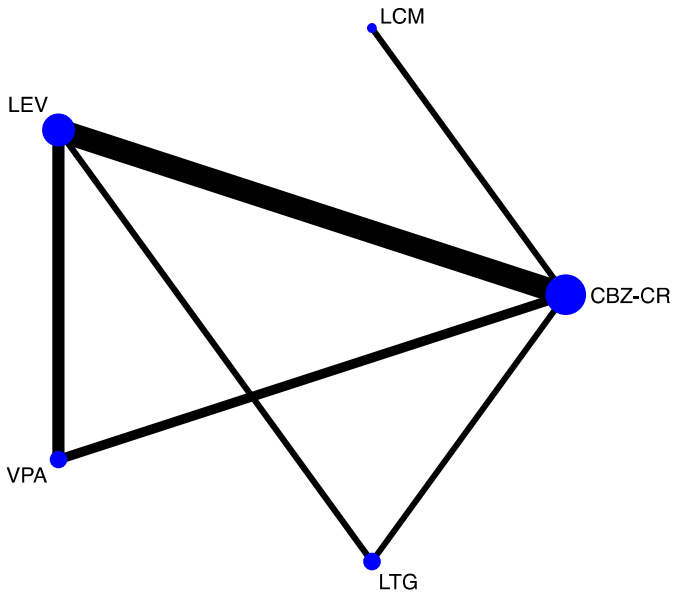
c) Withdrawal for any cause at 12 months



d) Withdrawal for any adverse event at 12 months



e) Any adverse event at 12 months

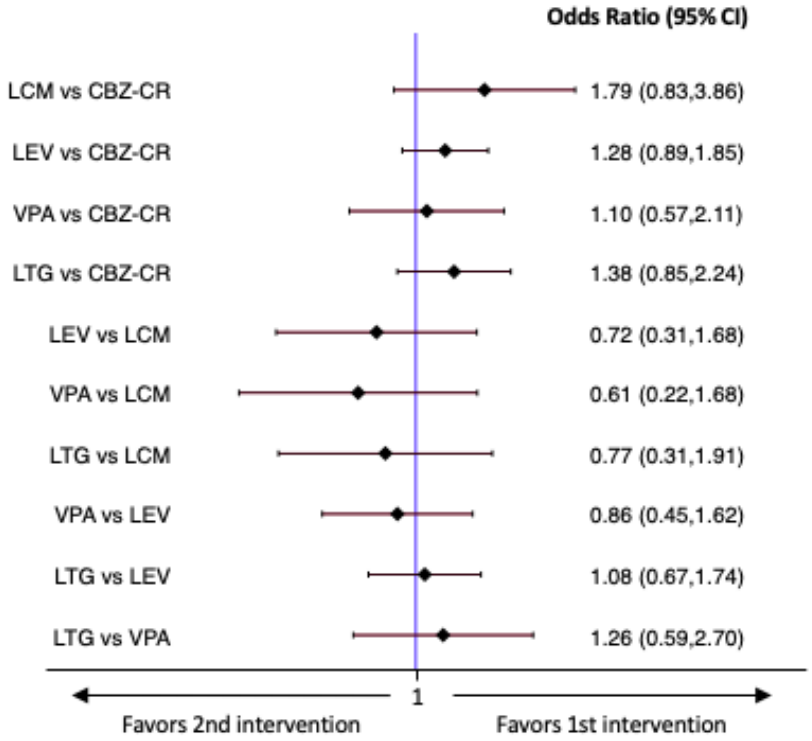


The width of the lines is proportional to the inverse of the variance of the comparison treatment effect and the size of every circle is proportional to the number of randomly assigned participants.

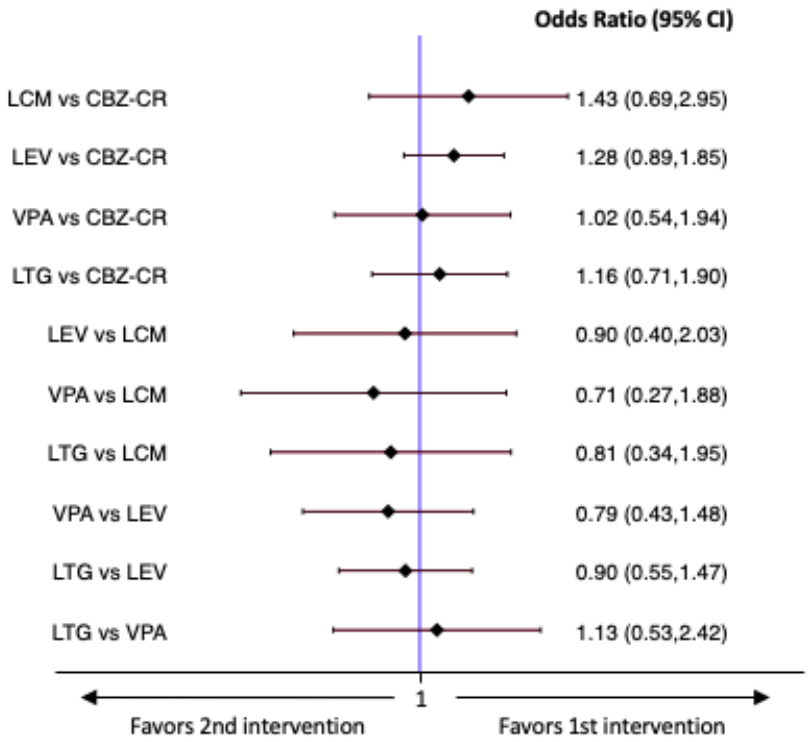
Abbreviations: CBZ-CR: carbamazepine controlled-release; CBZ-IR: carbamazepine immediate-release; GBP: gabapentin; LCM: lacosamide; LEV: levetiracetam; LTG: lamotrigine; PHT: phenytoin; VPA: valproic acid.

Figure 3. Interval plots for the efficacy and safety outcomes

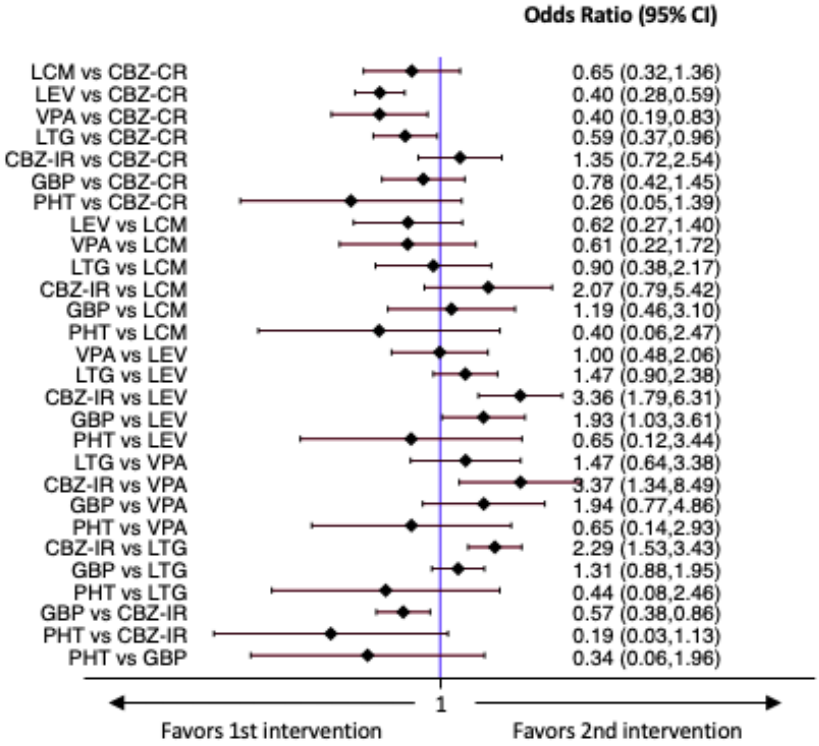
a) Seizure freedom at 6 months



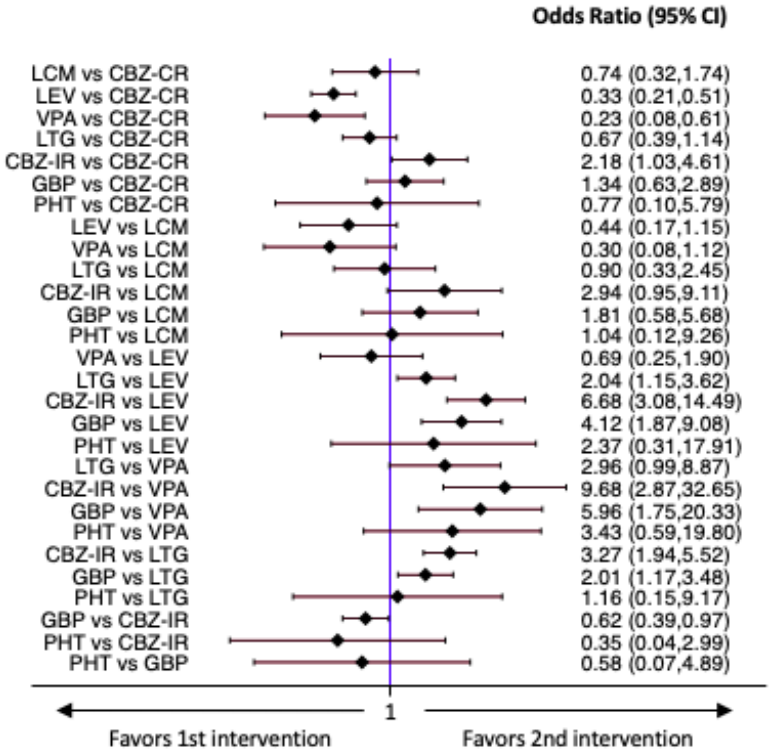
b) Seizure freedom at 12 months



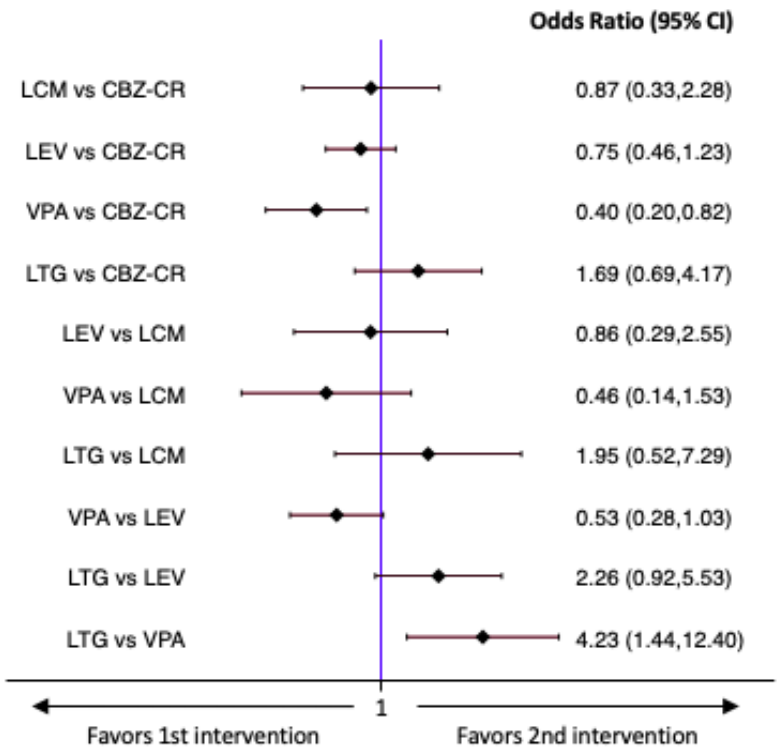
c) Withdrawal for any cause at 12 months



d) Withdrawal for any adverse event at 12 months



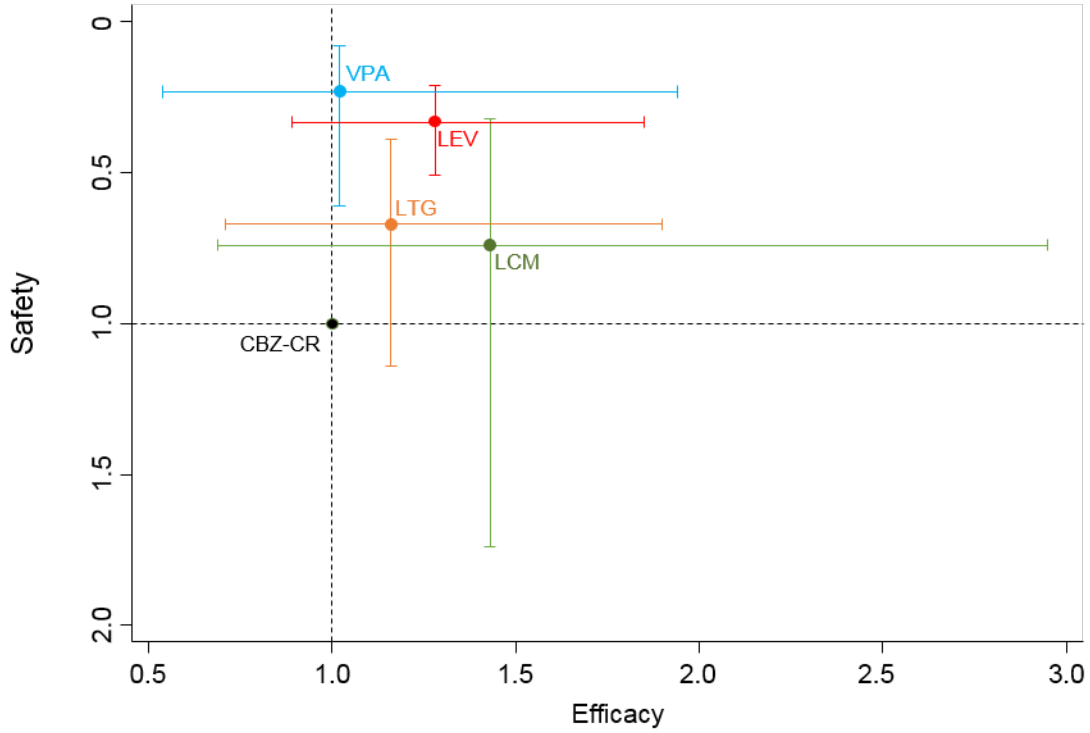
e) Any adverse event at 12 months



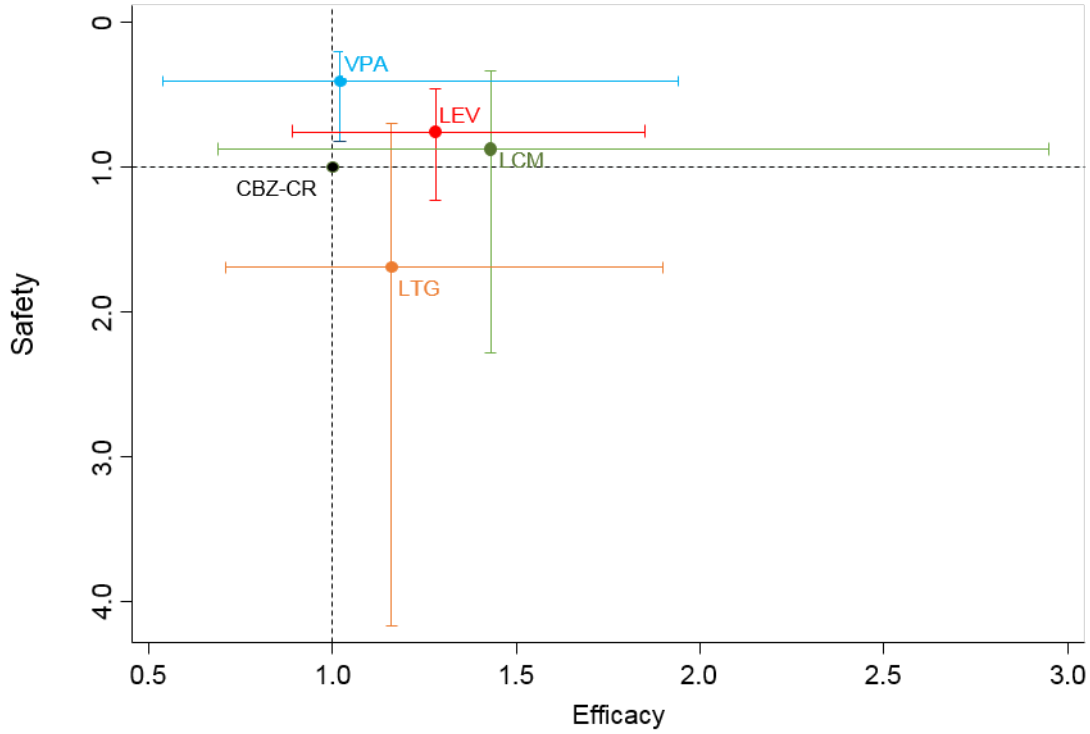
Abbreviations: CBZ-CR: carbamazepine controlled-release; CBZ-IR: carbamazepine immediate-release; GBP: gabapentin; LCM: lacosamide; LEV: levetiracetam; LTG: lamotrigine; PHT: phenytoin; VPA: valproic acid.

Figure e-1. Two-dimensional graphs of efficacy versus tolerability at 12 months

A) Seizure freedom versus withdrawal for any adverse event



B) Seizure freedom versus occurrence of any adverse event



Effect sizes for individual drugs are represented by colored nodes, with bars representing corresponding 95% confidence intervals.

Table e-1: Results of the pairwise meta-analyses for the efficacy and safety outcomes

a) Seizure freedom at 6 months

Comparison	Study	Odds ratio (95% CI)	p value
LCM vs. CBZ-CR	Baulac et al., 2017	1.79 (0.83-3.86)	0.138
LEV vs. CBZ-CR	Pohlmann-Eden et al., 2016; Werhahn et al., 2015	1.28 (0.89-1.85)	0.181
VPA vs. CBZ-CR	Pohlmann-Eden et al., 2016	1.02 (0.51-2.03)	0.966
VPA vs. LEV	Pohlmann-Eden et al., 2016	0.90 (0.47-1.74)	0.761
LTG vs. CBZ-CR	Werhahn et al., 2015	1.48 (0.88-2.47)	0.139
LTG vs. LEV	Werhahn et al., 2015	1.01 (0.61-1.69)	0.956

b) Seizure freedom at 12 months

Comparison	Study	Odds ratio (95% CI)	p value
LCM vs. CBZ-CR	Baulac et al., 2017	1.43 (0.69-2.95)	0.335
LEV vs. CBZ-CR	Pohlmann-Eden et al., 2016; Werhahn et al., 2015	1.28 (0.89-1.85)	0.180
VPA vs. CBZ-CR	Pohlmann-Eden et al., 2016	0.94 (0.48-1.85)	0.855
VPA vs. LEV	Pohlmann-Eden et al., 2016	0.84 (0.44-1.60)	0.596
LTG vs. CBZ-CR	Werhahn et al., 2015	1.25 (0.73-2.13)	0.411
LTG vs. LEV	Werhahn et al., 2015	0.84 (0.50-1.41)	0.513

c) Withdrawal for any cause at 12 months

Comparison	Study	Odds ratio (95% CI)	p value
LCM vs. CBZ-CR	Baulac et al., 2017	0.65 (0.32-1.36)	0.254
PHT vs. VPA	Craig et al., 1994	0.66 (0.14-2.93)	0.575
LEV vs. CBZ-CR	Pohlmann-Eden et al., 2016; Werhahn et al., 2015	0.40 (0.28-0.59)	<0.001

VPA vs. CBZ-CR	Pohlmann-Eden et al., 2016	0.34 (0.16-0.73)	0.005
VPA vs. LEV	Pohlmann-Eden et al., 2016	1.71 (0.55-2.49)	0.682
CBZ-IR vs. LTG	Rowan et al., 2005	2.29 (1.533-3.43)	<0.001
GBP vs. LTG	Rowan et al., 2005	1.31 (0.88-1.96)	0.177
GBP vs. CBZ-IR	Rowan et al., 2005	0.57 (0.38-0.86)	0.007
LTG vs. CBZ-CR	Werhahn et al., 2005	0.68 (0.41-1.13)	0.135
LTG vs. LEV	Werhahn et al., 2015	1.28 (0.76-2.14)	0.353

d) Withdrawal for any adverse event at 12 months

Comparison	Study	Odds ratio (95% CI)	p value
LCM vs. CBZ-CR	Baulac et al., 2017	0.74 (0.32-1.74)	0.493
PHT vs. VPA	Craig et al., 1994	3.43 (0.59-19.80)	0.168
LEV vs. CBZ-CR	Pohlmann-Eden et al., 2016; Werhahn et al., 2015	0.33 (0.21-0.51)	<0.001
VPA vs. CBZ-CR	Pohlmann-Eden et al., 2016	0.20 (0.07-0.54)	0.002
VPA vs. LEV	Pohlmann-Eden et al., 2016	0.85 (0.30.2.42)	0.753
CBZ-IR vs. LTG	Rowan et al., 2005	3. 27 (1.94-5.52)	<0.001
GBP vs. LTG	Rowan et al., 2005	2.02 (1.17-3.48)	0.012
GBP vs. CBZ-IR	Rowan et al., 2005	0.62 (0.39-0.97)	0.037
LTG vs. CBZ-CR	Werhahn et al., 2005	0.75 (0.43-1.31)	0.312
LTG vs. LEV	Werhahn et al., 2015	1.71 (0.92-3.20)	0.091

e) Any adverse event at 12 months

Comparison	Study	Odds ratio (95% CI)	p value
LCM vs. CBZ-CR	Baulac et al., 2017	0.87 (0.33-2.28)	0.776

LEV vs. CBZ-CR	Pohlmann-Eden et al., 2016; Werhahn et al., 2015	0.75 (0.46-1.23)	0.256
VPA vs. CBZ-CR	Pohlmann-Eden et al., 2016	0.37 (0.17-0.79)	0.010
VPA vs. LEV	Pohlmann-Eden et al., 2016	0.56 (0.28-1.10)	0.091
LTG vs. CBZ-CR	Werhahn et al., 2015	1.89 (0.72-4.92)	0.191
LTG vs. LEV	Werhahn et al., 2015	2.04 (0.79-5.24)	0.140

Abbreviations**:** AED: antiepileptic drug; CBZ: carbamazepine; CBZ-CR: carbamazepine controlled-release; CBZ-IR: carbamazepine immediate-release; CI: confidence interval; GBP: gabapentin; LCM: lacosamide; LEV: levetiracetam; LTG: lamotrigine; OR: odds ratio; PHT: phenytoin; VPA: valproic acid.

Appendix I: PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix II: Search strategy for different databases

EMBASE and MEDLINE:
'elderly randomized' OR (('elderly'/exp OR elderly) AND 'randomized controlled trial' AND (epilep* OR seizur*))

CENTRAL:
elderly (epilep* OR seizur*)

Opengrey.eu
elderly (epilep* OR seizur*)

Appendix III: Excluded studies with reasons for exclusion

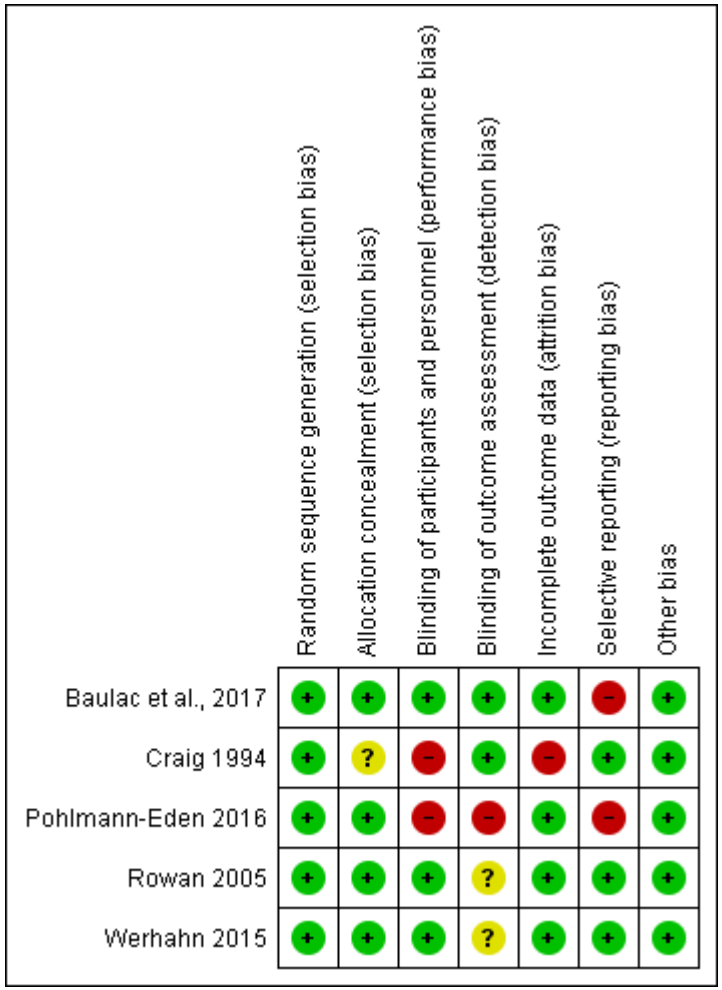
Study	Reference	Reason(s) for exclusion
Nieto-Barrera et al., 2001	Epilepsy Res 2001;46:145–55	Timepoints for outcome assessment different from inclusion criteria
Gilad et al., 2007	Clin Neuropharmacol. 2007; 30:189– 95.	Etiology-specific epilepsy (stroke)
Saetre et al., 2007	Epilepsia 2007;48:1292–302	Timepoints for outcome assessment different from inclusion criteria
Ramsay et al., 2008	*Epilepsia. 2008;59:1180-5*	No monotherapy trial
Cumbo et al., 2010	*Epilepsy Behav. 2010;17:461-6*	Timepoints for outcome assessment different from inclusion criteria; etiology-specific epilepsy (dementia)
Zhang et al., 2011	*J Int Med Res. 2011;39:408-15*	No monotherapy trial
Consoli et al., 2012	Cerebrovasc Dis. 2012;34:282– 9	Etiology-specific epilepsy (stroke)
Leppik et al., 2014	Epilepsy Res. 2015;110:216–20	No monotherapy trial
Brodie et al., 2016	Epilepsy Res. 2016;127:114–8	No monotherapy trial

Appendix IV: Assessment of risk of bias, adopted from the Cochrane Handbook

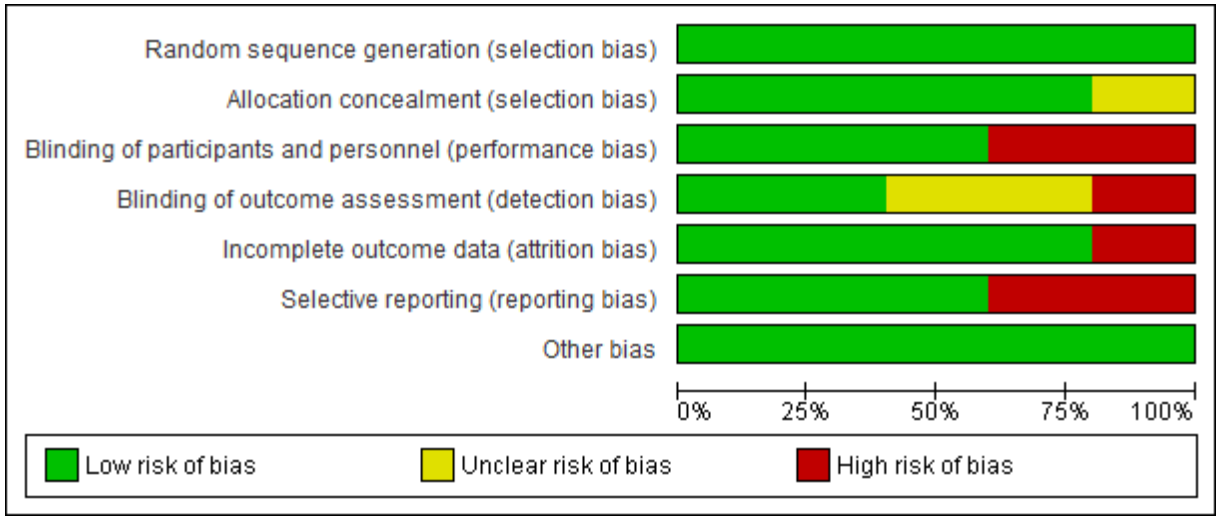
Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. Higgins JPT and Green S, editors. The Cochrane Collaboration, 2011. Available at http://handbook-5-1.cochrane.org/.

Domain and corresponding risk of bias	**Description**
Generation of a randomised sequence (***selection bias***, biased allocation to interventions)	The investigators describe the method used to generate the sequence generation process in sufficient detail to allow an assessment of whether it should produce comparable groups.
Allocation concealment (***selection bias***, biased allocation to interventions due to inadequate concealment of allocations prior to assignment)	The investigators describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.
Blinding of participants and personnel (***performance bias*** due to knowledge of the allocated interventions by participants and personnel during the study)	The investigators describe the method used to blind study participants and personnel to prevent them from knowing the allocated interventions.
Blinding of outcome assessment (***detection bias*** due to knowledge of the allocated interventions by outcome assessors)	The investigators describe the method used to blind outcome assessors to prevent them from knowing the allocated interventions.
Incomplete outcome data (***attrition bias*** due to amount, nature or handling of incomplete outcome data.)	The outcome data is complete for each participants with regard to each outcome. Missing outcome data or exclusions from the analysis are taken into consideration, assessing their potential impact on the study results.
Selective reporting (***reporting bias*** due to selective outcome reporting)	The published reports include all expected outcomes, including those that were pre-specified.

Appendix V: Summary of risk of bias in included studies

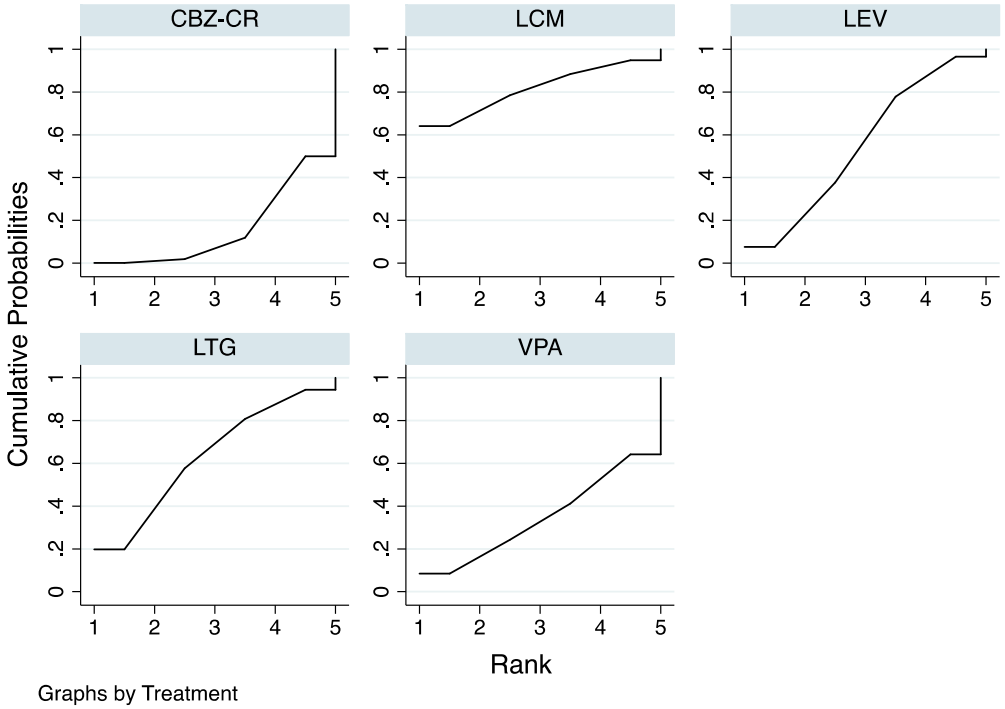


Appendix VI: Risk of bias graph (review authors' judgements about each risk of bias item presented as percentages across all included studies)

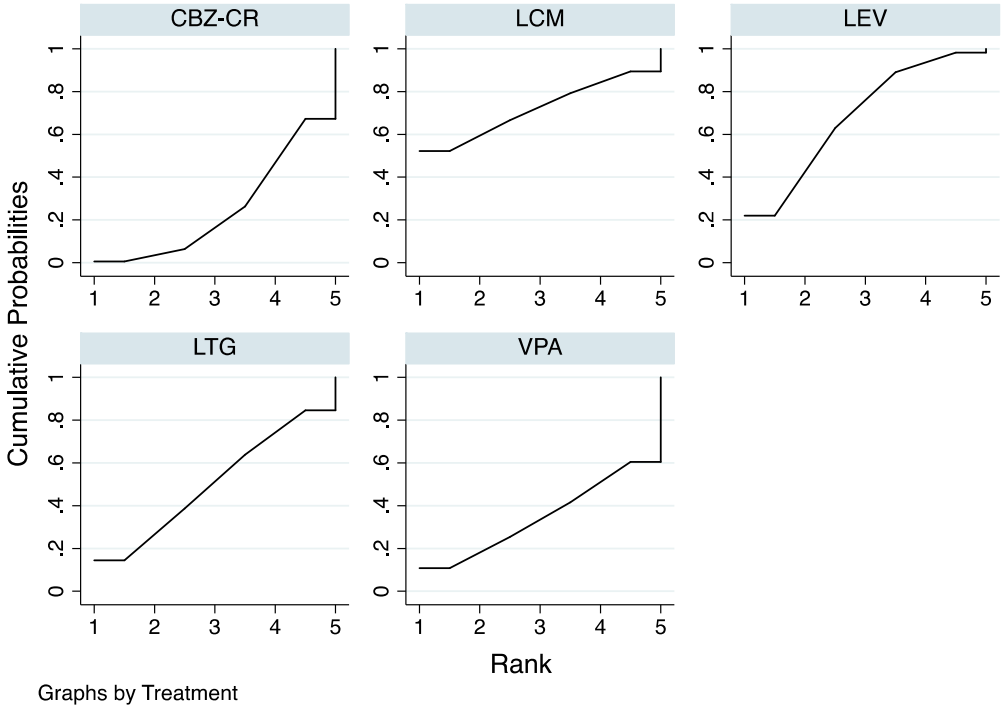


Appendix VII: Ranking according to SUCRA for the efficacy and safety outcomes

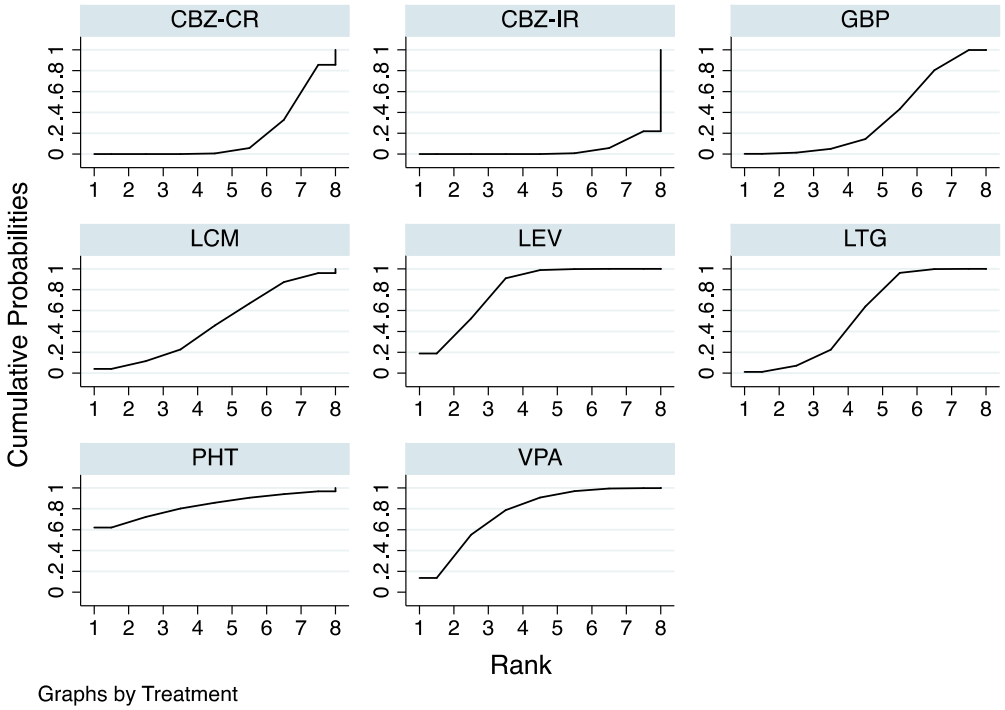
f) Seizure freedom at 6 months



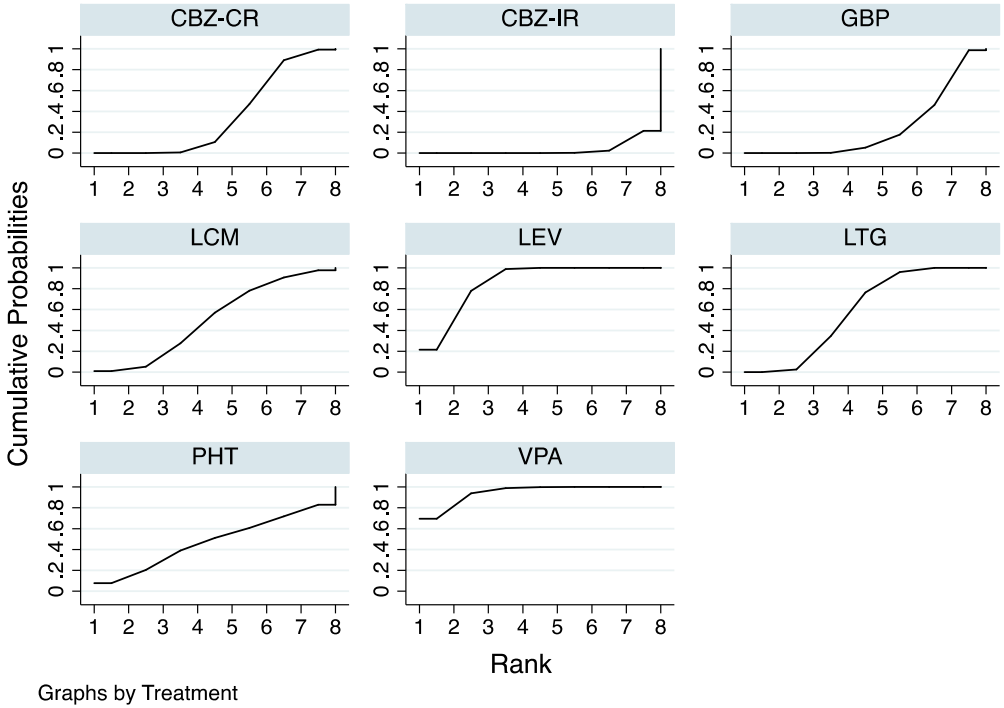
g) Seizure freedom at 12 months



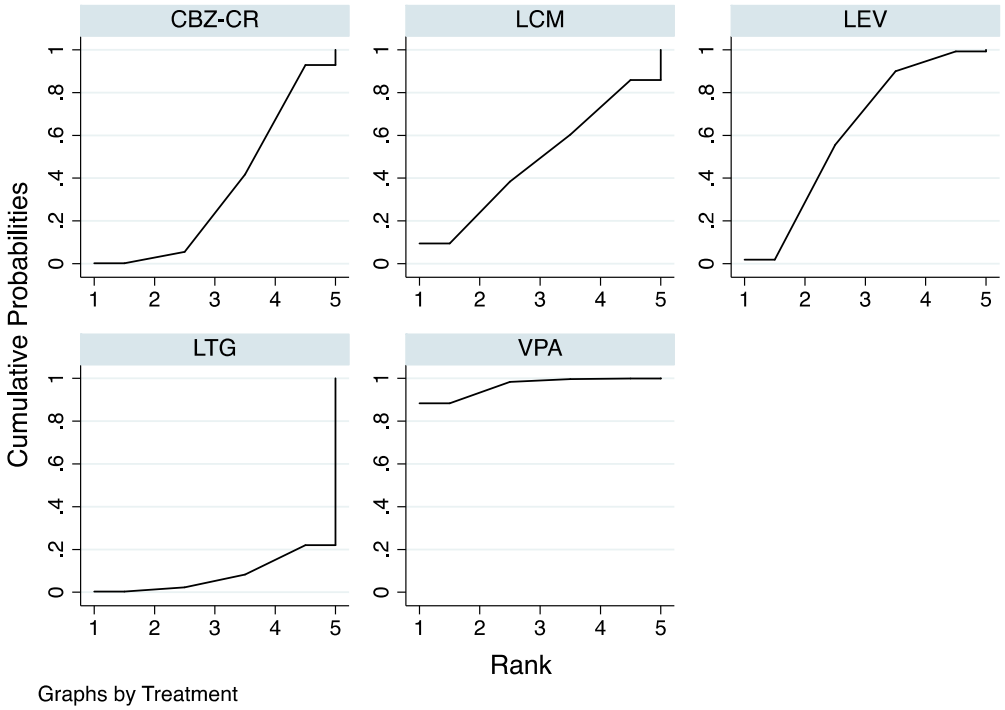
h) Withdrawal for any cause at 12 months



i) Withdrawal for any adverse event at 12 months



j) Any adverse event at 12 months



Abbreviation: SUCRA:surface under the cumulative ranking curve.

Appendix VIII: Details of carbamazepine preparation and manufacturing drug company

Study	CBZ formulation	Carbamazepine preparation and manufacturing drug company
Rowan et al., 2005[14]	CBZ-IR	NR
Werhahn et al., 2015[15]	CBZ-CR	Carbamazepine Sandoz Retard 200 mg tablets (Sandoz International GmbH, Holzkirchen, Germany); subsequently replaced by bioequivalent Tegretol® Retard by Novartis, Basel, Switzerland during the study since the firs became unavailable
Pohlmann-Eden et al., 2016[16]	CBZ-CR	Novartis, Switzerland
Baulac et al., 2017[17]; Rosenow et al., 2017[19]	CBZ-CR	Tegretol® Retard Tablets 200 mg

Abbreviations: CBZ-CR: carbamazepine controlled-release; CBZ-IR: carbamazepine immediate-release; NR: not explicitly reported.